MP10-21 ASSOCIATION OF OBESITY WITH INCREASED ENDOGENOUS OXALATE SYNTHESIS

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Introduction

Urinary oxalate levels are affected by both dietary and endogenous components. Prior studies have demonstrated the positive correlation between weight/body mass index (BMI) and urinary oxalate excretion. Our objective was to determine if this association is secondary to increased endogenous oxalate synthesis.

Methods

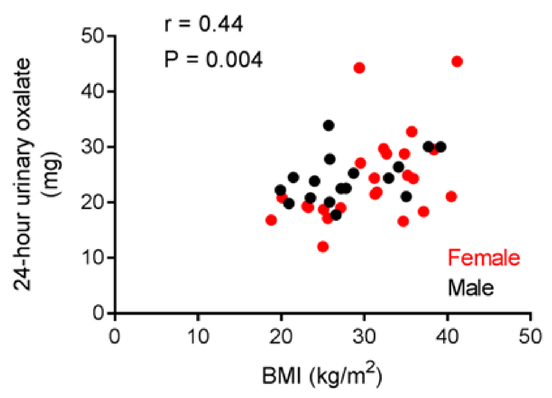
Healthy subjects, between 18 and 65 years old, with variable BMI were recruited. Subjects consumed a low oxalate controlled diet containing 16% protein, 30% fat, 54% carbohydrate, 1000 mg calcium, and 30 mg oxalate which was devoid of vitamin C and calcium supplements. Subjects remained on this diet for 3 days. 24-hour urine collections were performed on the last two days. Urinary oxalate was measured by ion chromatography coupled with mass spectroscopy. Statistical analysis included Chi-squared, correlation and linear regression analysis, and student t-test.

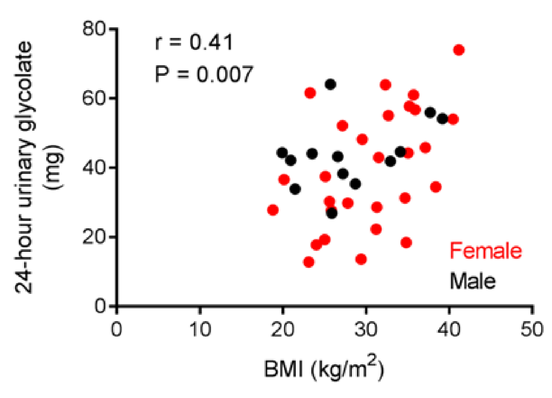
Results

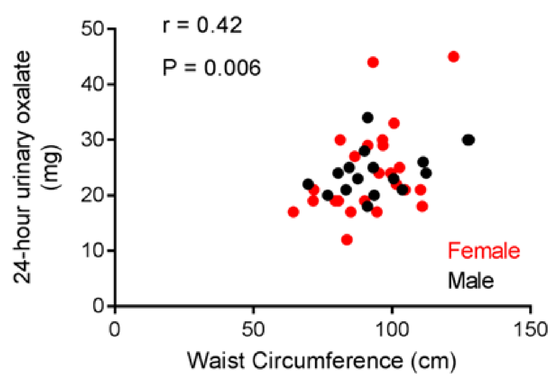
There were 41 subjects recruited with various BMIs (19-42). Urinary oxalate excretion (mg/day) was positively correlated with BMI (r=0.44, p=0.004) and waist circumference (r=0.42, p=0.006). Similar correlations were see with urinary glycolate excretion (mg/day) with BMI (r=0.41, p=0.007) and waist circumference (r=0.36, p=0.02).

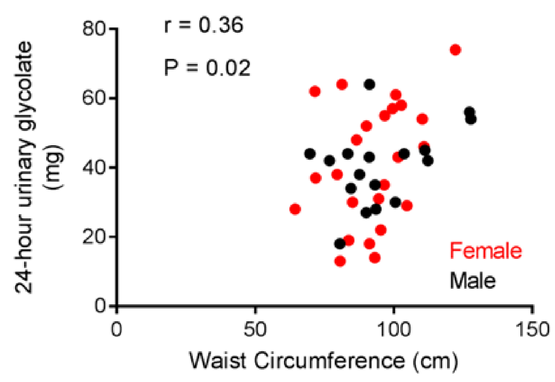
Discussion

These results demonstrate a positive correlation between urinary oxalate derived from endogenous oxalate synthesis and BMI as well as other measures of obesity. This also provides an explanation for the association between stone risk and obesity.









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THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

MP2-21 URINARY OXALATE EXCRETION IN OBESE MOUSE MODEL

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Introduction

Studies have demonstrated the positive correlation between body weight/BMI and urinary oxalate excretion. We hypothesize that this is due to increased endogenous oxalate synthesis. This was studied in two models of obesity, ob+/ob+ mice and wild type mice fed a high fat diet.

Methods

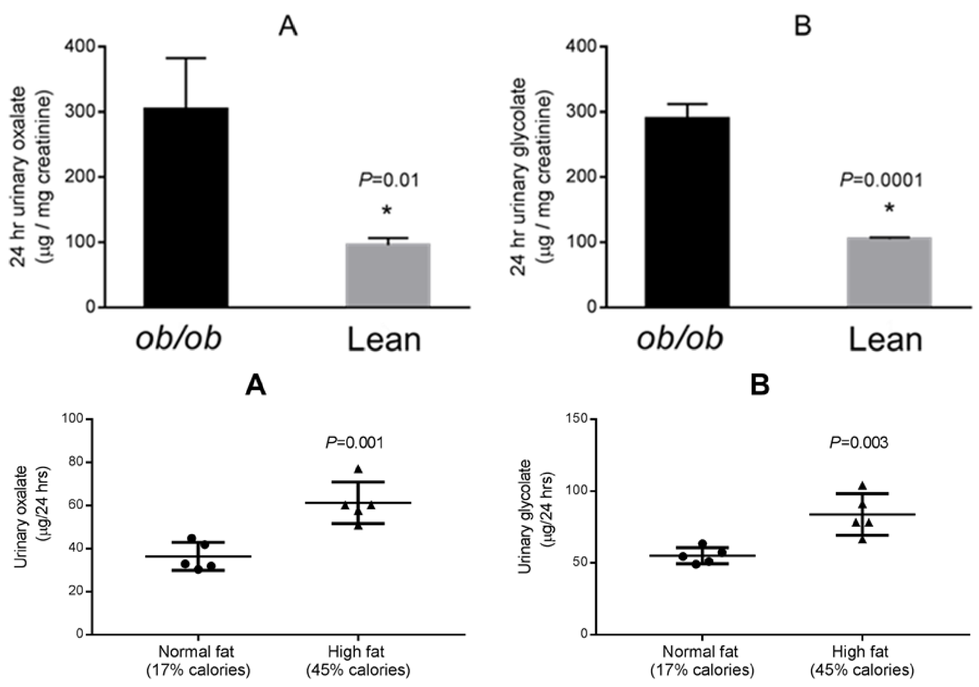
Wild type (WT) controls (n=5), high fat diet (HFD) (n=5), ob+/ob- lean controls (n=3), and ob+/ob+ (n=3) mice were fed a diet ultra-low in oxalate (<10µg/g diet) and glycolate (<3µg/g diet) and housed in metabolic cages. In the high fat diet, 45% of calories was fat vs 17% in normal diet. While on controlled diets the WT and HFD mice were administered a subcutaneous bolus of 2 µmoles 13C2-glycolate (oxalate precursor). 24 hour urine samples were collected. Ion chromatography coupled with mass spectroscopy was used to measure oxalate and glycolate isoptomers.

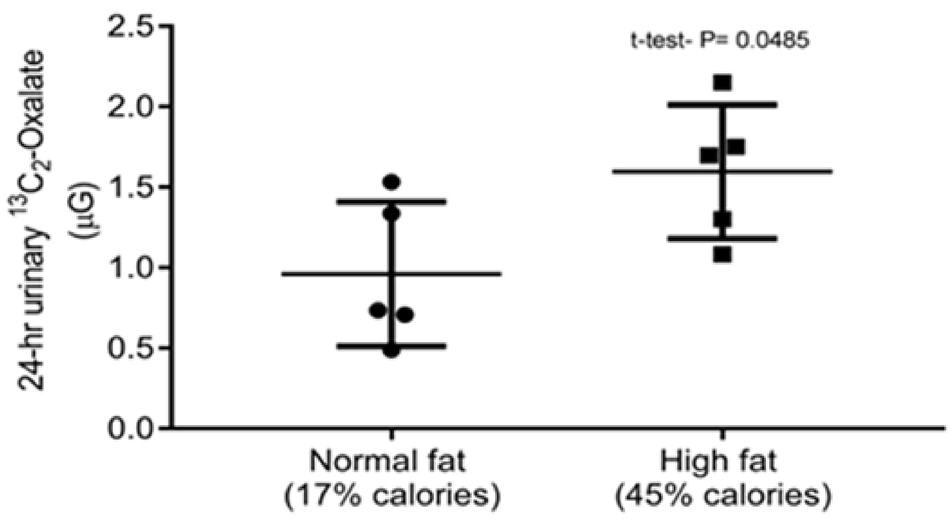
Results

HFD mice weight compared to control was 42.1 g vs 30.5 g (p=0.0002). 24 hour urinary oxalate excretion indexed to urinary creatinine (Cr) was significantly higher in the ob+/ob+ mice and the HFD mice relative to the comparative control mice, 303.3 vs 95.6 µg/mg Cr (ob+/ob+ versus ob+/ob-),p=0.01 and 133.1 vs 106.2 µg/mg Cr (HFD versus WT), p=0.003. 24 hour urinary glycolate excretion was also significantly higher in each, 289.5 vs 105.0 µg/mg Cr (ob+/ob+ versus ob+/ob-),p=0.0001 and 193.1 vs 166.2 (HFD versus WT), p=0.05. HFD mice produce more oxalate from glycolate following subcutaneous injection as measured by 13C2-oxalate levels, 1.5 vs 1.0 µg Cr, p=0.04.

Discussion

These findings suggest that obesity increases endogenous oxalate synthesis. Further studies are needed to understand the metabolic changes that occur in obesity.





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UP6-40 THE ASSOCIATION OF FATTY LIVER DISEASE AND URINARY OXALATE IN STONE FORMERS

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Introduction

Greater body mass index (BMI) increases the likelihood of a number of medical conditions including nephrolithiasis. Those with higher BMI are at increased risk of fatty liver disease. There is a positive correlation between urinary oxalate excretion (Uox) and BMI. Our objective was to determine if fatty liver disease is associated with increased Uox.

Methods

Twenty-four hour urinary oxalate excretion in 513 non-cystinuric, adult stone-formers (SF) who were also subjected to abdominal computed tomography (CT) or ultrasound imaging were correlated with the presence or absence of fatty liver disease. Complete. Statistical analysis included Chi-squared and student t-test.

Results

45% of SF were female. Majority of SFs were Caucasian (C) versus African American (AA) (88% vs 10%). 119 (23%) individuals were diagnosed with fatty liver disease. There was no difference between proportions of C and AAs diagnosed with fatty liver (19% vs 21%, $p=0.9$). SFs with fatty liver had higher Uox compared to those without (42.55 mg/d vs 37.73 mg/d, $p<0.009$). This finding remained significant in the male population (47.33 vs 40.97 mg/day, $p=0.005$), but not for females (34.21 vs 34.90, $p<0.82$). This relationship also remained significant for C population (43.64 vs 38.33 mg/day, $p<0.01$), but not the AA population (37.6 vs 32.9 mg/day, $p=0.20$).

Discussion

Among SFs, there is a positive correlation between presence of fatty liver disease and Uox. This finding is more pronounced in males and Caucasians. The reasons for these relationships need to be defined.

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UP6-57 SCREENING FOR PRIMARY HYPERPARATHYROIDISM IN A TERTIARY STONE CLINIC, A USEFUL ENDEAVOR

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Introduction

Primary Hyperparathyroidism (hPTH) is an endocrine disorder that can increase risk of nephrolithiasis. In addition, stone formers may have secondary hyperparathyroidism such as vitamin D deficiency or gastrointestinal mal-absorption. Our objective was to determine the prevalence amongst stone-formers evaluated at a tertiary stone clinic.

Methods

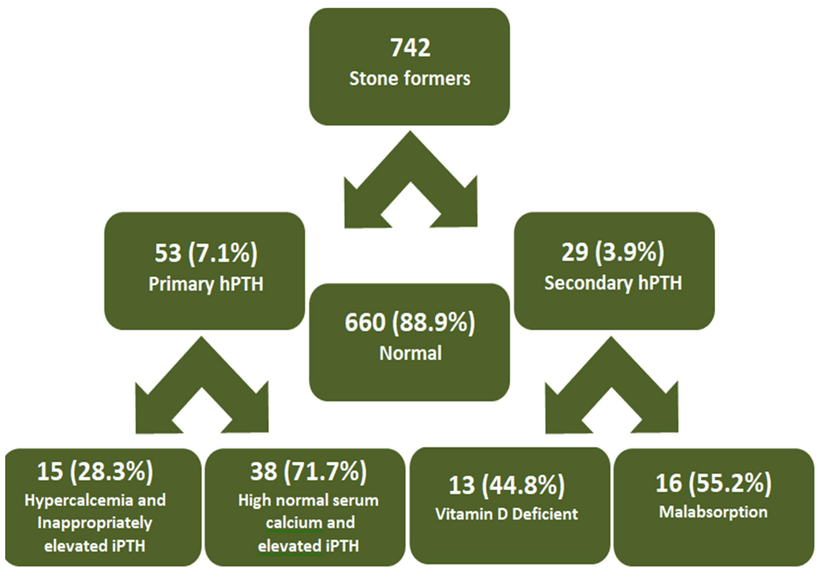
We retrospectively reviewed 742 adult stone formers seen by a single urologic surgeon from 2012-2017 all of whom were evaluated with intact serum PTH (iPTH) and serum calcium. The diagnosis of primary hyperparathyroidism was based on the presence of hypercalcemia with an inappropriately elevated iPTH or a high normal serum calcium and an elevated iPTH. These patients were devoid of vitamin D deficiency and gastrointestinal mal-absorption. The diagnosis was confirmed by surgical neck exploration in the majority.

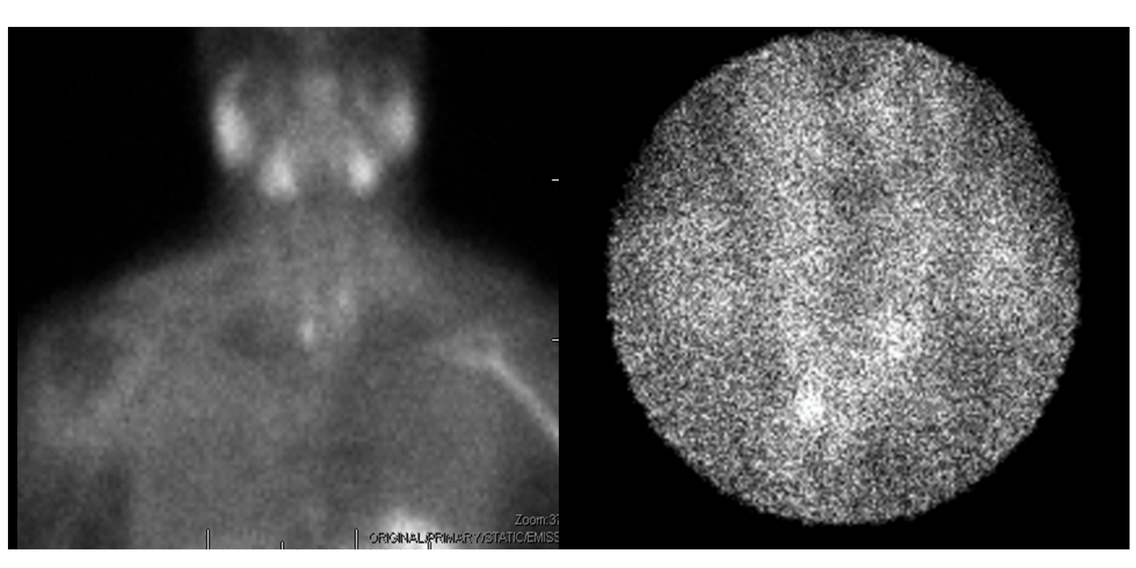
Results

Fifty-three (7.1%) were diagnosed with hPTH. Fifteen had hypercalcemia and inappropriately elevated iPTH, 38/53 (72%) had high normal serum calcium levels and inappropriately elevated iPTH. The potential diagnosis was ignored/missed by primary care physicians in 11 (20.8%) based on review of prior lab results.

Discussion

Primary hyperparathyroidism is very prevalent in our tertiary medical center kidney stone clinic, substantially higher than previous reports. Whether this is unique to patients in our region or due to referral bias needs to be further investigated. Furthermore, these results underscore the importance of scrutinizing the calcium parathyroid axis. In addition, primary care physicians need to be further educated regarding the association of primary hyperparathyroidism and kidney stone disease.





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MP2-20: RNA INTERFERENCE OF HEAPTIC LACTATE DEHYDROGENASE REDUCES URINARY OXALATE IN A MOUSE MODEL OF PRIMARY HYPEROXALURIA TYPE 1

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Introduction

Endogenous oxalate synthesis primarily occurs via lactate dehydrogenase (LDH) activity in the liver. Liver specific RNAi therapeutics are currently in clinical trials for a number of diseases. Previous work using RNAi against liver glycolate oxidase demonstrated reduction of urinary oxalate in the Agxt knock out mouse, a model for primary hyperoxaluria Type 1 (PH1). Our objective was to evaluate the effects of siRNA knock down of liver LDHA in a PH1 mouse model (Agxt knock out (KO)).

Methods

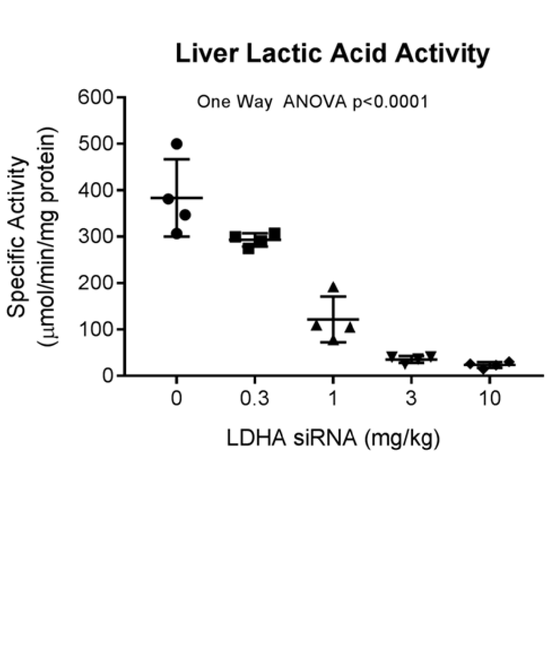
Agxt KO mice (n=6 for each group) were placed on an ultra-low oxalate diet. The mice were subcutaneously administered various doses of LDHA siRNA (Alnylam Pharmaceuticals). 24-hour urine samples were collected at baseline and weekly following LDHA siRNA treatment. Plasma, liver and muscle tissue were collected at completion of the study. Urinary, plasma, and tissue metabolites were measured using ion chromatography/mass spectrometry and high pressure liquid chromatography. LDH specific activity was determined in tissue lysates with either lactate or glyoxylate as the assay substrate and measuring the rate of reduction of NAD at 340nm at pH 9.0. Statistical analysis was performed utilizing Student t-test.

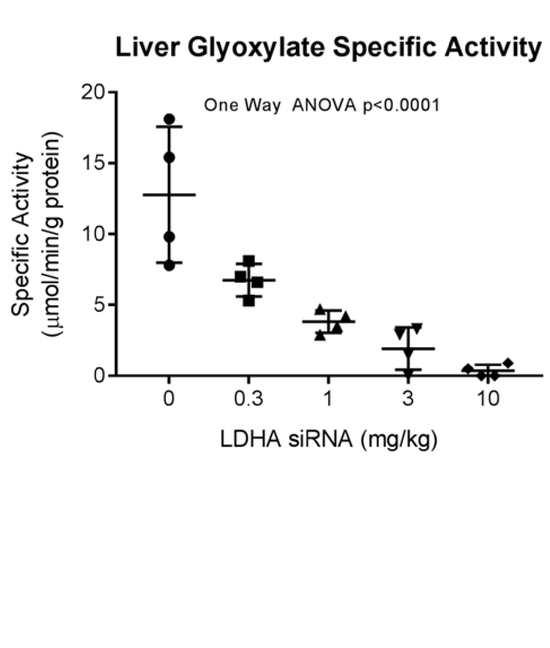
Results

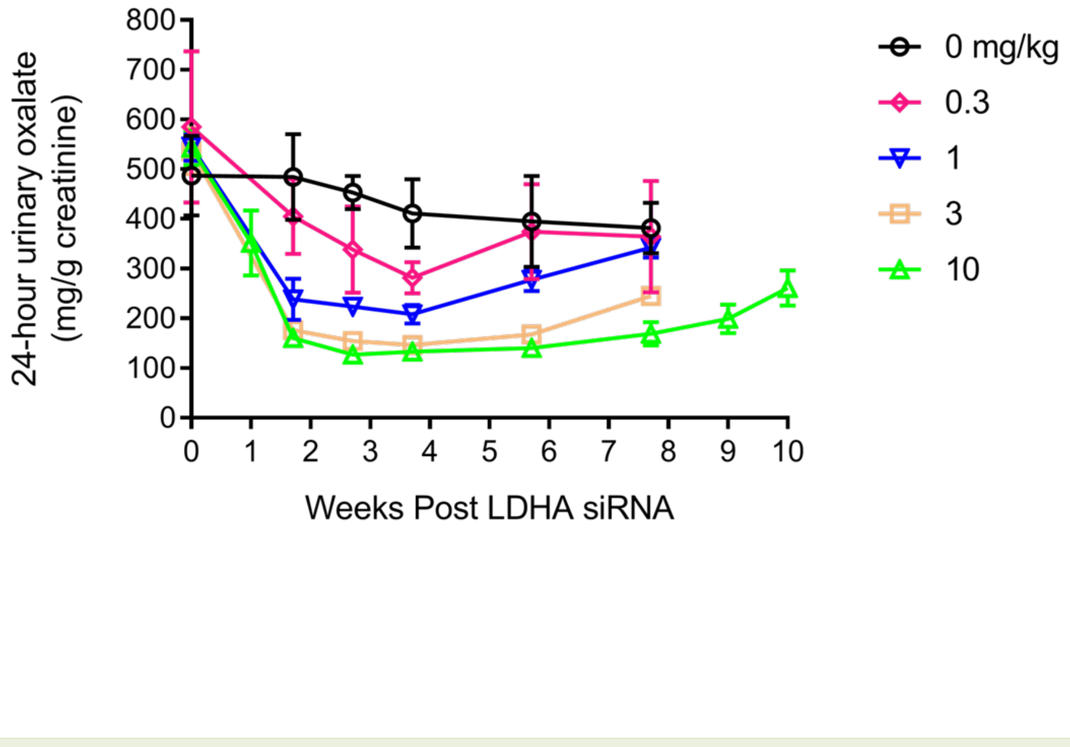
There was a decrease in liver specific LDH activity utilizing glyoxylate and lactate as a substrates. Decrease in activity was dose dependent. There was no change in LDH activity in muscle and heart tissue lysates following LDHA siRNA treatment. Decrease in urinary oxalate excretion was dose dependent and was normalized with increased dosing in a PH1 model.

Discussion

Knock down of hepatic LDHA using siRNA results in a profound decrease in urinary oxalate excretion in Agxt KO mice suggesting this approach may be an effective therapy for primary hyperoxaluria syndromes as well as idiopathic hyperoxaluria. The long-term consequences of a LDHA siRNA on liver metabolism warrants further investigation.







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